Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 3s, https://carcinogenesis.com/

Formulation and Evaluation of Solid Lipid Nanoparticle for Enhanced Solubility and Bioavailability of Poorly Soluble Efinaconazole Drug

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ABSTRACT

The objective of present investigation was to prepare & evaluate solid lipid nanoparticle (SLN) For Enhanced Solubility and Bioavailability of Poorly Soluble Efinaconazole Drug. SLN were formulated by High-shear hot homogenization and ultra-sonication method using stearic acid, Glyceryl monostearate, palmitic acid, and surfactants (1% and 2%). All the formulation was subjected to particle size, particle size distribution, zeta potential, scanning electron microscopy, crystallinity study by DSC and in-vitro release studies. It has been observed that, the high lipid concentration containing formulation have higher entrapment as compare to other two formulations. The SLN- dispersion shows 77.9±0.55% entrapment & zeta potential of the formulation was -31.1 which indicates the stability of formulation. The In-Vitro drug release rate of gel was evaluated using Modified franz diffusion cell containing dialysis membrane with phosphate buffer pH 7.4 as the receptor medium. It was concluded that the Efinaconazole loaded SLN formulation containing stearic acid, Glyceryl monostearate, palmitic acid, and surfactants (1% and 2%) shows much better result for Enhanced Solubility and Bioavailability of Poorly Soluble Efinaconazole Drug.

Keywords: Formulation, Evaluation, Solid Lipid Nanoparticle, Enhanced Solubility, Bioavailability and Efinaconazole Drug.

How to Cite: Mr. Rohit Krishna Pawar, Dr. Ramakant Sharma, (2025) Formulation and Evaluation of Solid Lipid Nanoparticle For Enhanced Solubility And Bioavailability of Poorly Soluble Efinaconazole Drug, Journal of Carcinogenesis, Vol.24, No.3s, 340-363.

1 INTRODUCTION

Nanoscale drug delivery systems (NDDS) have become essential instruments for improving the solubility and bioavailability of poorly soluble pharmaceuticals, thereby addressing significant challenges in pharmaceutical engineering concerning drug solubility and bioavailability. This review thoroughly encapsulates the research on nanodrug delivery systems (NDDS) aimed at enhancing the solubility and bioavailability of poorly soluble pharmaceuticals. We will first review the definition, categorization, and characteristics of poorly soluble pharmaceuticals, as well as the essential concepts, kinds, and attributes of Novel Drug Delivery Systems (NDDS). Poorly soluble medications are classified as BCS Class II and IV, both characterized by poor solubility but varied in permeability; BCS Class II pharmaceuticals possess more permeability than BCS Class IV, necessitating specific enhancement tactics for each class (1-3).

Nanodrug delivery systems (NDDS) employ the ultrafine dimensions, catalytic properties, and protective characteristics of nanomaterials to optimize drug administration, therefore improving drug efficacy and minimizing side responses. The systems may be categorized into six types: lipid-based nanoparticles (LNPs), polymer-based nanoparticles, nanoemulsions, nanogels, inorganic nanoparticles, and dendrimer-based nanoparticles. LNPs have demonstrated the ability to trigger apoptosis in liver cancer cells, hence augmenting medication effectiveness and presenting potential research implications for cancer treatment. Polymer-based nanoparticles demonstrate superior bacterial targeting, improving ocular adhesion and corneal permeability, indicating enhanced efficacy in the treatment of bacterial keratitis and other bacterial infections. Nanoemulsions, utilized as oral drug carriers, have markedly enhanced bioavailability compared to other mediums,

underscoring their promise as better carriers for oral pharmaceuticals (4, 5).

Nanogels provide targeted, prolonged medication delivery. Inorganic nanoparticles, which catalyse the production of highly cytotoxic agents such as BCS Class IV, synergize with chemotherapeutic agents like Doxorubicin (DOX) to eradicate cancer cells, presenting novel strategies for effective cancer therapy. Dendrimer-based nanoparticles, upon conjugation with the anticancer agent 5-fluorouracil, facilitate the progressive release of free 5-fluorouracil, therefore mitigating adverse medication effects and demonstrating significant potential for application as innovative nanomaterials (6-8). Our examination of nanonisation techniques, surface modification technologies, and carrier-mediated strategies reveals that NDDS can effectively improve the solubility of poorly soluble medicines. Nanonisation methods surmount biological obstacles such as the blood-brain barrier and nasal transport barriers, hence enhancing medication delivery efficacy and facilitating novel administration pathways. Surface modification, which alters the physicochemical features of nanoparticle surfaces, improves cellular targeting and hence promotes therapeutic efficacy. Carrier-mediated technology entails encapsulating weakly soluble compounds into high-solubility carriers, facilitating cellular absorption by passive diffusion, membrane fusion, and endocytosis. Furthermore, NDDS augment cellular absorption, facilitate intracellular release, and inhibit premature drug degradation, hence enhancing bioavailability (9, 10). Despite obstacles related to production costs and safety, nanomaterials have distinctive beneficial features absent in most other drug delivery materials, offering the potential to surmount the constraints of conventional delivery techniques and materials. Notably, NDDS have lately attracted heightened scientific interest in the medical domain. Conventional drug delivery systems frequently need repeated or elevated dosages to attain therapeutic outcomes, resulting in diminished overall effectiveness and patient adherence. Conversely, the utilization of nanotechnology-based medication delivery systems is gaining preference and undergoing extensive investigation. Research indicates that regulating particle size and altering components in nanoscale drug delivery systems can improve drug solubility, manage drug release, extend circulation duration, decrease drug clearance rates, selectively augment cellular uptake, and reduce adverse effects, thereby improving therapeutic efficacy (11-13).

2 MATERIAL AND METHODOLOGY

2.1 Preformulation Study

This chapter covers preformulation study, nano particle preparation, bio availability study design and data handling, optimization of bio analytical methods for estimating Efinaconazole in rat plasma samples, standard and sample solutions, in vitro dissolution methods, in vivo data analysis, and statistical analysis of pharmacokinetic data. General preformulation involves all steps and research needed to turn an active pharmacological substance into a dosage form. Physical and chemical properties of drugs alone and with excipients are examined. In this work, nano particle evaluation, in vitro dissolving method development, and drug-excipient compatibility were determined (14).

2.1.1 Physical appearance

The selected drug Efinaconazole was subjected to Preformulation studies to check the colour and appearance (15).

2.1.2 Melting point

The digital melting point device measured Efinaconazole's melting point. The capillary was sealed by placing it over a flame, and the Efinaconazole was inserted up to 1 cm and kept in the instrument's capillary holder. While heated at 5°C/min, Efinaconazole was monitored for melting (16).

2.1.3 Solubility studies

Efinaconazole was dissolved in various solvents by adding excess medication to 10 ml liquids in conical flasks. Flasks were held at 25± 0.5ºC in an isothermal shaker for 72 hours to achieve equilibrium. Equilibrated samples were centrifuged at 4000 rpm for 15 min after shaking. The supernatant liquid was filtered using a 0.45 µm membrane. The concentration of Efinaconazole was measured in the supernatant liquid after dilution at λmax = 258 nm (17).

2.1.4 Differential Scanning Calorimetry

Differential scanning calorimetry examined drug–excipient interaction. Pure Efinaconazole, excipients, and drug excipient combinations have DSC thermograms. The pharmaceutical industry uses Thermogravimetric and differential scanning calorimetry (DSC) to determine drug and excipient molecule stability, purity, and formulation compatibility (18).

2.1.5 Compatibility Studies

We used infrared spectral matching to detect any chemical interaction between Efinaconazole, lipid, and surfactants. Drug-excipient (1:1) physical combinations were combined with 400 mg potassium bromide (IR grade). A hydraulic press at 15 tons compressed 100 mg of the mixture into a clear pellet. The Shimadzu FT-IR spectrophotometer scanned the samples from 4000 to 400 cm^{-1}. Sample appearance and spectra peak appearance/disappearance were monitored to determine physical and chemical interactions (19).

2.1.6 Development of calibration curve

Dissolving 100 mg of Efinaconazole in 10 ml of 0.1N HCl and making up to 100 ml with various buffers (pH 6.8, pH 7.4) at 1 mg/ml yielded a stock solution. The stock solution was diluted to 5-25 µg/ml and measured at 258 nm, the wave length of maximum absorption (λmax). The λmax of the medication was measured using a UV-Visible spectrophotometer, scanning between 200 and 400 nm. At λmax of 258 nm, all solutions were tested for absorbance against a blank, and the calibration curve between concentration and absorbance was plotted (20).

2.2 Formulation Development of Efinaconazole SLN

2.2.1 Selection of Lipids

In 5 ml vials, surplus API was dissolved in 200mg of palmitic acid, stearic acid, Glyceryl monostearate, Glyceryl monooleate, cetylpalmitate, and cholesterol to assess Efinaconazole solubility. Samples were vortexed and agitated in an EXPO HI-TECH isothermal shaker for 72 hours at 37± 1.0 ºC to achieve equilibrium. API was added in 10mg increments until solubilization stopped. The supernatant was separated from equilibrated samples after 15 minutes of centrifugation at 3500 rpm. The UV spectrophotometer measured medication dissolution in each sample. The most soluble lipids were used to make SLN (21).

2.2.2 Selection of Surfactants

After selecting the lipid by solubilization technique the SLN were be prepared by using different grades of polysorbates namely tween 20, tween 40, tween 80 and SLN will be evaluated. The surfactants were selected based on the literature survey (22).

2.2.3 Preparation of SLNs

High-shear hot homogenization and ultra-sonication produced Efinaconazole-loaded SLN. Initial lipids included stearic acid, Glyceryl monostearate, palmitic acid, and surfactants (1% and 2%). Efinaconazole was combined with lipid and soya lecithin in the organic phase and heated to 70ºC to dissolve the drug lipid phase. Similar temperatures were applied to the surfactant-containing aqueous phase. Later, heated lipid solution was added and homogenized with a mechanical stirrer for 30 minutes to create a transparent solution. Later, the solution was sonicated for 25 minutes to create evenly sized SLN. This standard process was used to create SLN with variable lipid and surfactant amounts as shown in table 1. Cosurfactant concentration was constant throughout formulations (23).

Table 1 The formula for the preparation of Solid lipid Nanoparticles of Efinaconazole

Formula	Drug % w/w	Lipid	The concentration of Lipid % w/w	Co surfactant %w/w	Emulsifying Agent name	Concentration of Emulsifying Agent %w/w
F1	0.1	Stearic Acid	1	0.5	Tween 20	1
F2	0.1	Stearic Acid	1	0.5	Tween 20	2
F3	0.1	GMS	1	0.5	Tween 20	1
F4	0.1	GMS	1	0.5	Tween 20	2
F5	0.1	Palmitic Acid	1	0.5	Tween 20	1
F6	0.1	Palmitic Acid	1	0.5	Tween 20	2
B1	0.1	Stearic Acid	1	0.5	Tween 40	1
B2	0.1	Stearic Acid	1	0.5	Tween 40	2
B3	0.1	GMS	1	0.5	Tween 40	1
B4	0.1	GMS	1	0.5	Tween 40	2
B5	0.1	Palmitic Acid	1	0.5	Tween 40	1
B6	0.1	Palmitic Acid	1	0.5	Tween 40	2
A1	0.1	Stearic Acid	1	0.5	Tween 8 0	1

A2	0.1	Stearic Acid	1	0.5	Tween 80	2
A3	0.1	GMS	1	0.5	Tween 80	1
A4	0.1	GMS	1	0.5	Tween 80	2
A5	0.1	Palmitic Acid	1	0.5	Tween 80	1
A6	0.1	Palmitic Acid	1	0.5	Tween 80	2

2.3 Characterization of SLN of Efinaconazole (24-27)

2.3.1 Infrared studies (FTIR)

Efinaconazole and lipid compatibility was investigated by FTIR spectroscopy of their physical mixes. Infrared investigations were done on physical combinations at 4000–400 cm^{-1}. The main functional group skeleton of Efinaconazole was studied. Fourier transform infrared spectroscopy (FTIR) produces an infrared spectrum of solid, liquid, or gas absorption or emission. The FTIR spectrometer concurrently captures high-resolution spectral data across a wide range.

2.3.2 Particle size and zeta potential

The particle size of Efinaconazole-loaded SLN was measured by DLS in a Zetasizer 9DTS Ver.5.10, Malvern). To assess preparation uniformity, SLN polydispersity index (PDI) was investigated. Particle size analysis by zeta sizer included surface charge. Particle size and zeta potential are crucial to understanding particle behavior in colloidal systems and nanomaterials. Zeta potential is a particle's surface electrical charge, which affects its stability and interactions with other particles. Particle size is its physical dimensions.

2.3.3 Entrapment efficiency

Drug entrapment in nanosystems depends on entrapment efficiency. Many tests are needed to assure medication retention in nanocarriers. Centrifugation measured free unloaded medication in the formulation. The formulation was centrifuged at 10,000 RPM to separate the supernatant. The supernatant contains the formulation's unloaded drug, which was measured spectro-photometrically, and entrapment efficiency was examined.

The EE was determined as follows:

LC = [(weight of Efinaconazole in SLN)/ (weight of SLN)] × 100%

EE = [(weight of Efinaconazole in SLN)/ (weight of Efinaconazole added)] × 100%

Weight of Efinaconazole in SLN = Total drug content - free drug content

2.3.4 Drug dissolution release

Dialysis bag technique (pore size: 2.4nm; mol. wt. cut off: 12,000-14,000 Daltons) measured in-vitro drug release. Before dissolving, the membrane was immersed in clean water for 12 hours. The dialysis bag contained 5mg of Efinaconazole, accurately weighed. This was then put in a beaker with 250ml of phosphate buffer for dissolving. Drug release was studied in a 37.50C beaker at 50RPM for 12 hours. At 0.5, 1, 2, 4, 6, 8, 12 h, 1ml of samples was changed with new buffer. Filtered sample evaluated at 258nm by UV spectroscopy.

2.3.5 Morphology of SLNs

Solid lipid nanoparticles (SLNs) are spherical and 10–1000 nm in size. They have a solid lipid core and a surfactant layer in aqueous solution. The morphology is affected by lipids, surfactants, and preparation method. SLNs' exterior topography was studied using scanning electron microscopy (Hitachi, Japan). Samples were distributed on the conducting stub for electron-focused imaging.

2.3.6 Drug Content

The drug content was evaluated by taking blank equivalent to the common weight of the SLN. After weighing sample, the drug was extracted in water for 6 hours. The solution was filtered and the absorbance was calculated at 258nm to quantify the amount of Efinaconazole.

2.3.7 Powdered x-ray diffraction study

Continuous scan mode was used for SLN X-ray analysis, with a sample width of 0.010̣ (2) and a scanning speed of 10/min. Expert proanalytical diffractometer evaluated at 30kv and 15mA. The samples were tested from 0-1000. Powder X-ray diffraction (XRD) analyses crystalline structures. The diffraction pattern from X-raying a powdered material is analysed. The material's phase, crystallinity, and unit cell dimensions are revealed by its fingerprint. Pharmaceuticals, materials science, and mineralogy use it to detect unknown chemicals and characterize materials.

2.3.8 Transmission electron microscopy (TEM)

The external electron topography of particle was determined by TEM (Hiachi, 2000, Japan). The drug loaded SLN were dispersed in of phosphotungsic acid 2% and was finely spreaded over conducting slab to study the morphology. The working principle of the Transmission Electron Microscope (TEM) is similar to the light microscope. The major difference is that light microscopes use light rays to focus and produce an image while the TEM uses a beam of electrons to focus on the specimen, to produce an image (28).

2.3.9 Stability studies

Stability studies are experiments designed to assess how environmental conditions affect a product's quality, safety, and efficacy over time. These studies are crucial in various industries, including pharmaceuticals, food and beverage, and cosmetics, to determine shelf life, appropriate storage conditions, and to ensure product integrity throughout its lifecycle. The stability analysis of Efinaconazole loaded SLNs were conducted by storing them at room temperature (28±2°C), refrigerated at 3-5° C for 6 months. After the storage period, SLN were analyzed for average SLN size, surface charge, EE as well as PDI (29).

3 RESULT AND DISCUSSION

3.1 Preformulation Study

3.1.1 Physical description

Efinaconazole was observed for colour, Odour and physical state. It was observed that the sample was off white, odorless, and crystalline.

3.1.2 Melting point

Melting point of Efinaconazole was determined using capillary method. 3mm of capillary tube which was sealed at one end was filled with Efinaconazole. Capillary was introduced into the digital melting point apparatus. Melting point was noted from the temperature at which drug starts melting to the temperature at which entire sample melts. Melting point: about 225 °C (with decomposition).

3.1.3 Determination of λmax of Efinaconazole Drug

UV-visible spectrophotometry has been used to identify various drugs to obtain specific information related to the chromophoric part of the molecule. When exposed to light in the UV-visible region of the spectrum, organic molecules in solution absorb light of a particular wavelength depending on the type of electronic transition associated with the absorption. The drug (10 mg) was accurately weighed and dissolved in methanol, and the volume was made up to 100 ml using a 100ml volumetric flask. Then, 1 ml of this stock solution was pipetted out into two 10 ml volumetric flask and volume were made up to 10 ml. The resulting solution was scanned between 200 – 400 nm using UV- Visible spectrophotometer. The λmax was found to be 258nm in Fig 1.

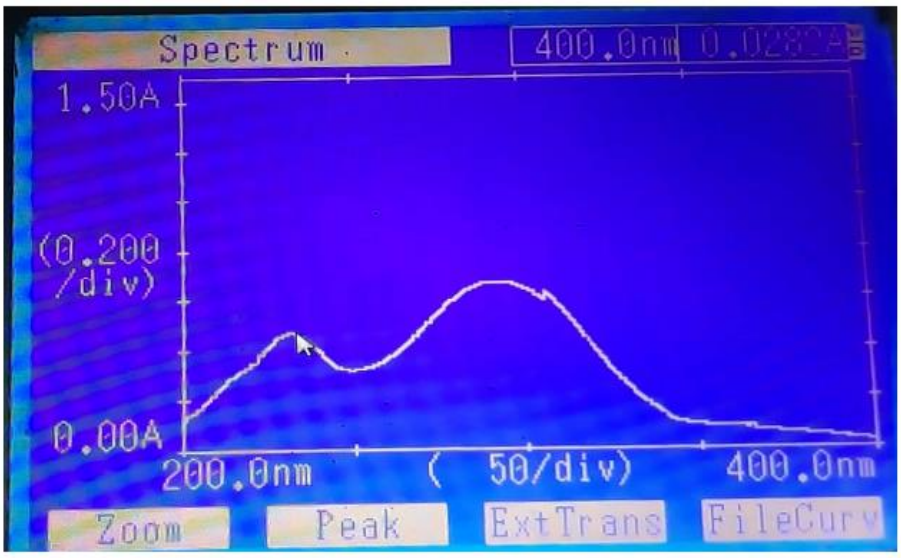


Figure 1 λmax determination by UV-Visible spectrophotometer

3.1.4 Preparation of Standard Curve Efinaconazole in Methanol at λmax 258 nm.

Efinaconazole was accurately weighed i.e. 10 mg in 10 ml of methanol and volume was made up to 100 ml with methanol in 100 ml volumetric flask. This resulted in 100 µg/ml stock solution so from that aliquots of 0.2 ml, 0.4 ml, 0.6, 0.8, 1.0,

1.2, 1.4, 1.6, 1.8 and 2.0 ml were prepared and volume was made up to 10 ml volumetric flask with methanol. These aliquots were analyzed at λmax 258 nm by using UV Visible spectrophotometer. The standard curve was plotted between absorbance and concentration.

Table 2 Standard curve data of Efinaconazole in methanol solution

Concentration (µg/ml)	Absorbance (in methanol)
2	0.147
4	0.276
6	0.436
8	0.54
10	0.695
12	0.778
14	0.944
16	1.077
18	1.188
20	1.334

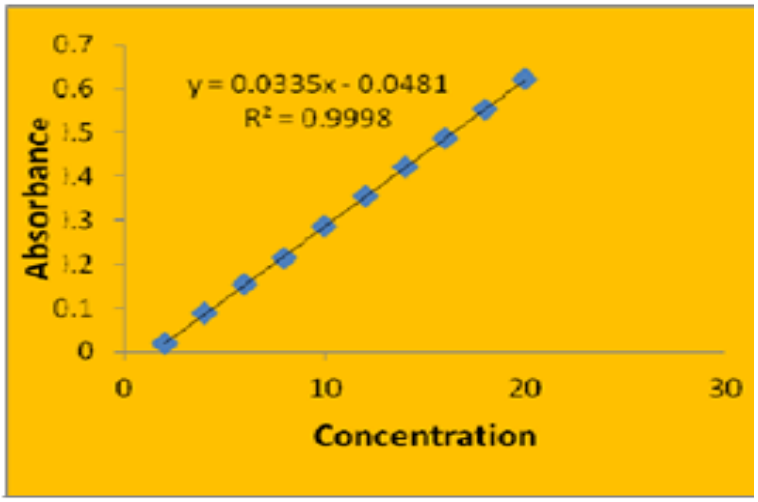


Figure 2 Standard curve of Efinaconazole in Methanol solution at λ_{max}=258nm

3.1.5 Preparation of Standard Curve of Efinaconazole in Methanol: PBS (30:70) pH 6.8 at λmax 258 nm.

Efinaconazole was accurately weighed i.e. 10 mg in 10 ml of methanol and volume was made up to 100 ml with mixture of methanol: PBS (pH 6.8) (30:70) in 100 ml volumetric flask. This resulted in 100 µg/ml stock solution so from that aliquots of 0.2 ml, 0.4 ml, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 ml were prepared and volume was made up to 10 ml volumetric flask with the mixture of methanol: PBS pH 6.8 (30:70). These aliquots were analyzed at λmax 258nm by using UV Visible spectrophotometer. The standard curve was plotted between absorbance and concentration.

Table 3 Standard curve data of Efinaconazole in methanol: PBS (30: 70) solution pH 6.8

Concentration (µg/ml)	Absorbance (in methanol)
2	0.147
4	0.276
6	0.436
8	0.54
10	0.695
12	0.778
14	0.944
16	1.077
18	1.188
20	1.334

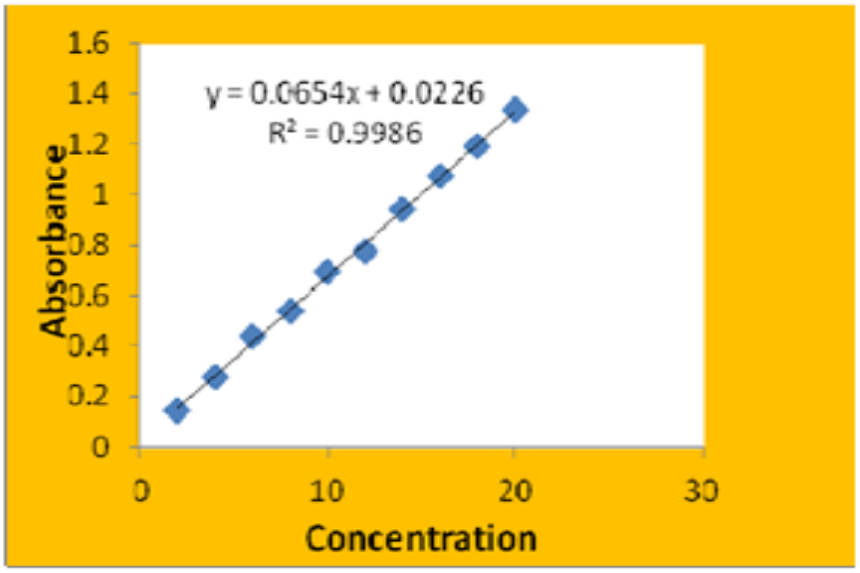


Table 4 Standard curve of Efinaconazole in methanol: PBS (30: 70) at λmax=258nm

3.1.6 Drug-excipients compatibility

Compatibility study is one of the most important factors in determining polymeric delivery effectiveness. Compatibility between drug and polymers due to interaction with no changes chemical and physical properties of the drug because each drug has its unique chemical and physical properties. Compatibility between drug and polymers is determined by various methods, such as Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) etc.

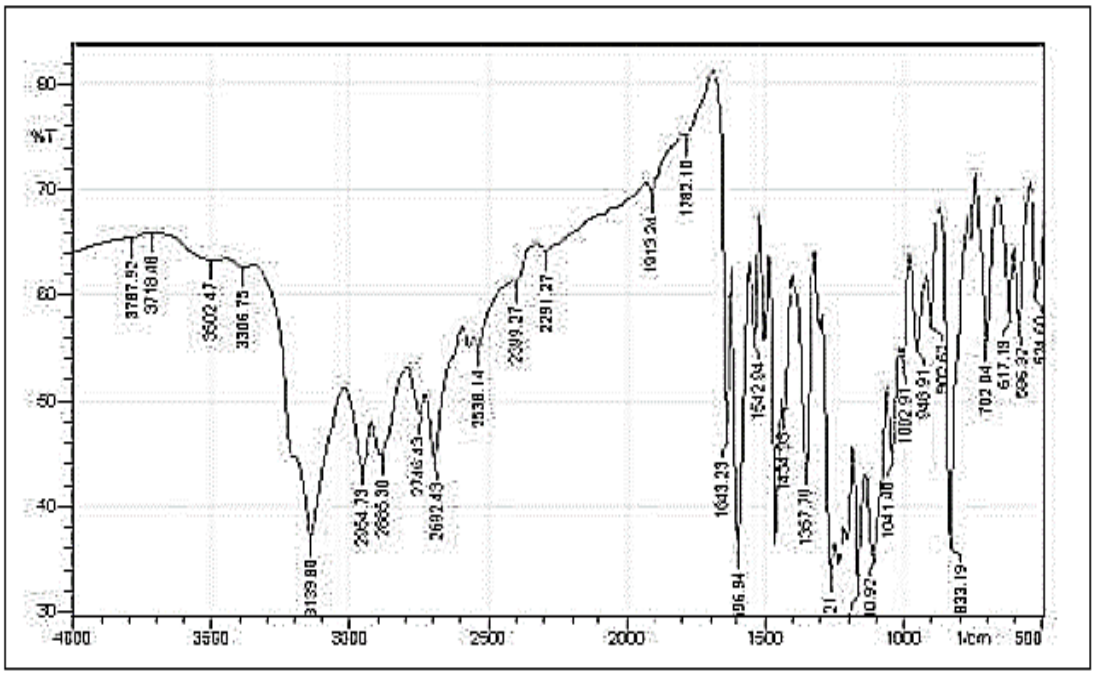


Figure 3 Reference FT IR spectra of Efinaconazole

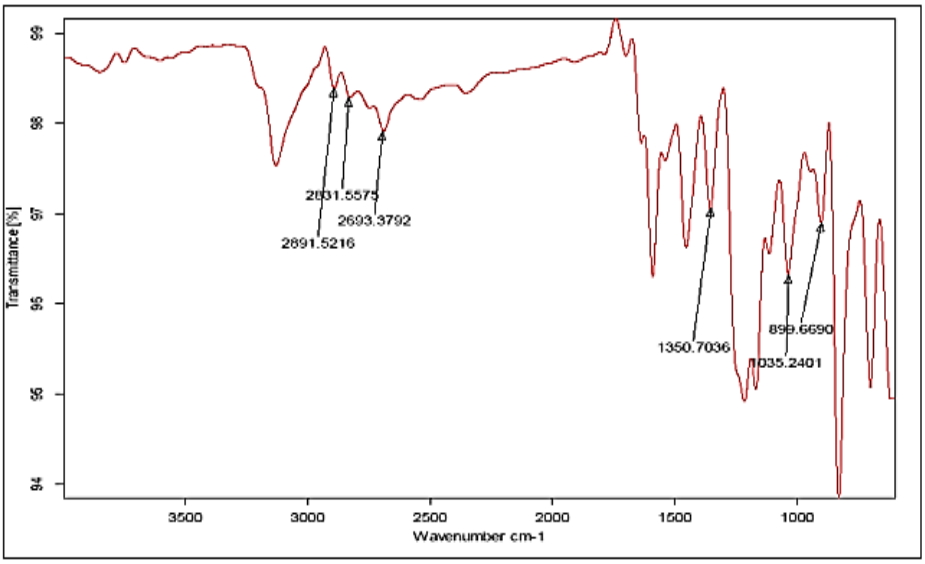


Figure 4 FTIR spectra of Efinaconazole (API)

The identification of pure drug (Efinaconazole) is performed with the help of FTIR spectroscopy. A comparative IR spectrum of pure Efinaconazole and reported reference spectrum Fig. 3 and 4 were found to be almost similar.

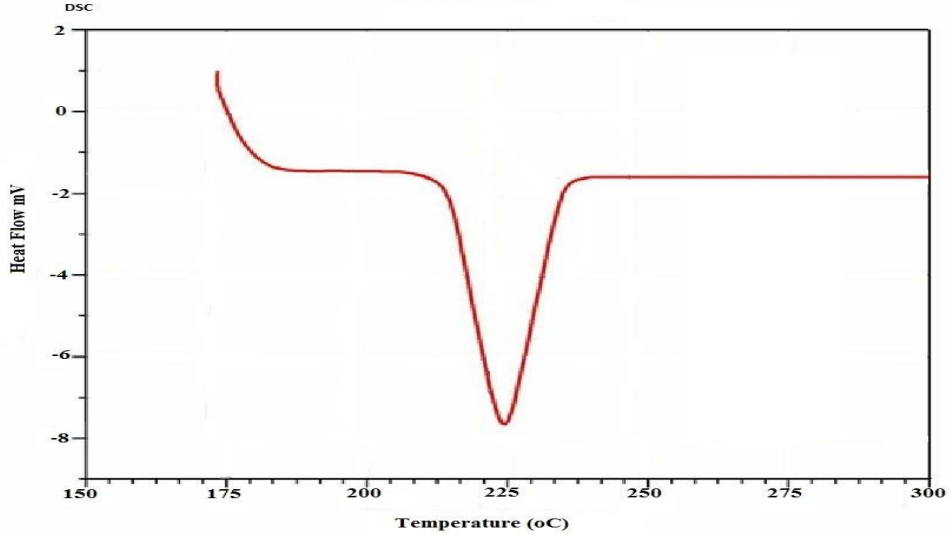


Figure 5 DSC Thermogram of Pure Efinaconazole (API)

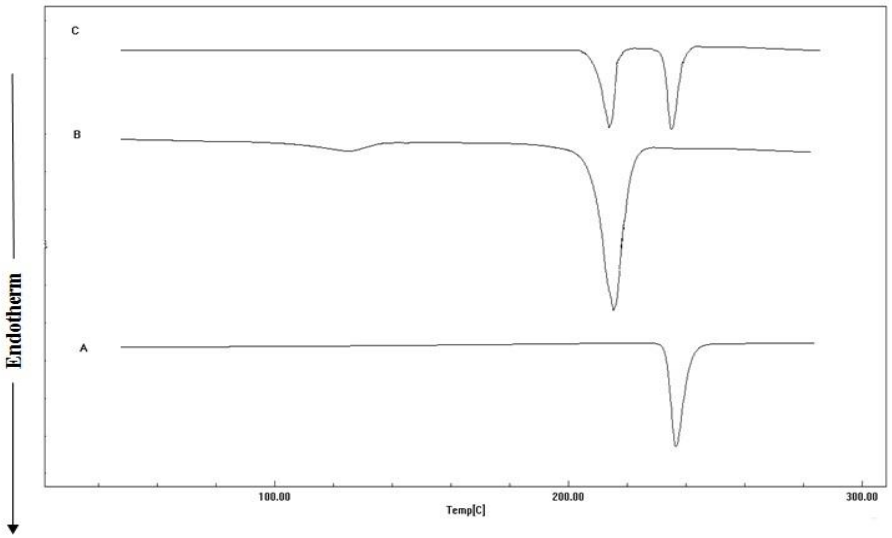


Figure 6 DSC thermogram of SLN formulation

3.2 Preparation of Efinaconazole SLNs

The selected Efinaconazole SLN formulations were formulated with varying concentration of Palmitic Acid and was shown in the table below

Table 5 Composition of Selected Efinaconazole SLN formulation of using Emulsifying Agent Tween 80 and Palmitic Acid

Formula	Drug % w/w	Lipid	Concentration of Lipid % w/w	Emulsifying Agent name	Concentration of Emulsifying Agent %w/w	Concentration of cosurfactant %w/w
EF1	0.10	Palmitic Acid	0.5	Tween 80	2	0.5
EF2	0.10	Palmitic Acid	1.0	Tween 80	2	0.5
EF3	0.10	Palmitic Acid	1.5	Tween 80	2	0.5
EF4	0.10	Palmitic Acid	2.0	Tween 80	2	0.5
EF5	0.20	Palmitic Acid	0.5	Tween 80	2	0.5
EF6	0.20	Palmitic Acid	1.0	Tween 80	2	0.5
EF7	0.20	Palmitic Acid	1.5	Tween 80	2	0.5
EF8	0.20	Palmitic Acid	2.0	Tween 80	2	0.5

3.3 Characterization of Efinaconazole SLNs

3.3.1 FTIR study of selected Efinaconazole SLN Formulation

Table 6 FTIR study of selected Efinaconazole SLN Formulation

Observed(cm^{-1})	Reported (cm^{-1})	Inference
3319.64	3500-3100	N-H Stretching
2849	2850-2100	C≡C(Alkyne)
1737.9	1750-1730	C=O of Ester
1305.5	1350-1000	C-N

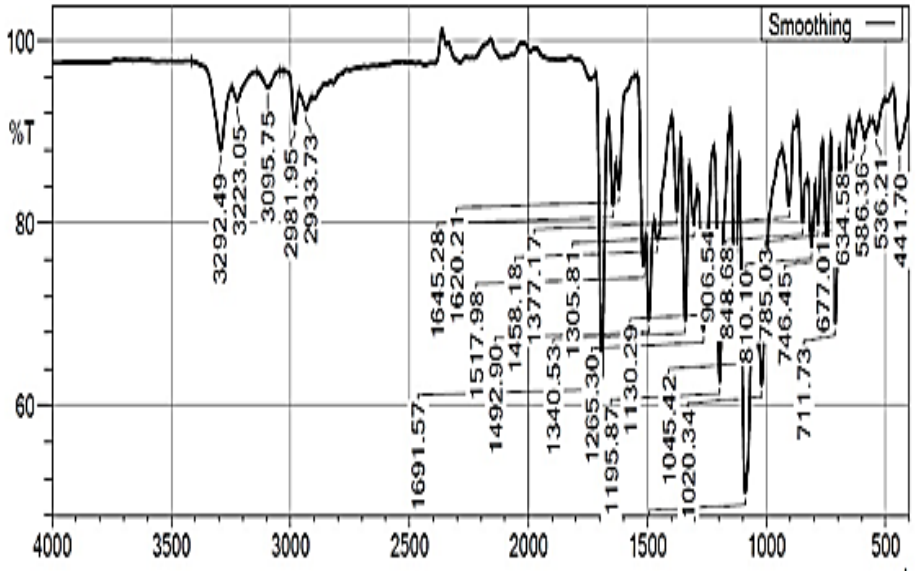


Figure 7 FTIR Spectrum of Pure Drug Efinaconazole

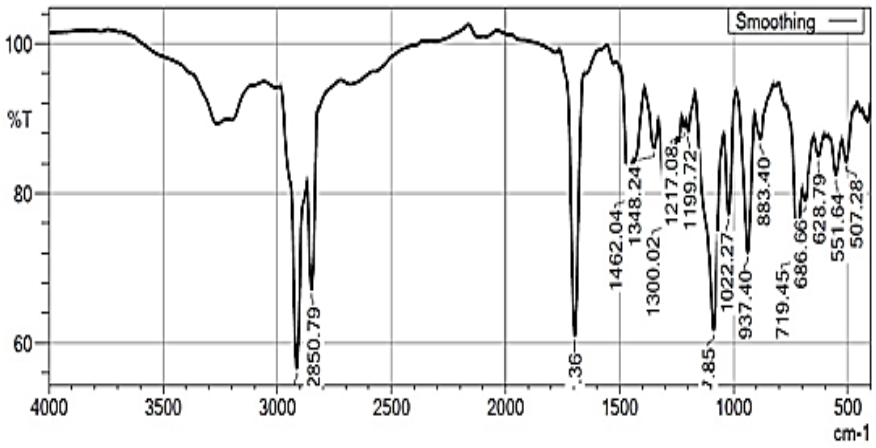


Figure 8 FTIR Spectrum of Efinaconazole SLN Formulation EF2

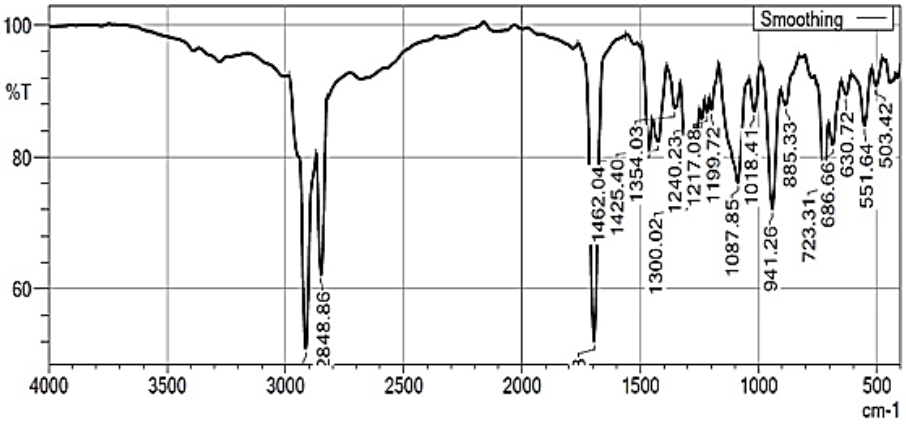


Figure 9 FTIR Spectrum of Efinaconazole SLN Formulation EF6

3.3.2 Particle size, Entrapment Efficiency, PDI, zeta potential of Efinaconazole loaded SLN formulations

The nanoparticle characterization parameters were mentioned in the table. The particle size was in the Nano range and was ranging from 191nm to 237 nm. Maximum EE was observed in the formulation EF6. All the particle exhibited negative surface charge around -36mV to -39mV. A similar trend was observed in the particle size and EE. The increased concentration of the tweens has increased the EE and decreased the particle size. Meanwhile, among the polysorbates used, tween 80 exhibited particles with smaller particle size and higher EE.

Table 7 Average particle size, zeta potential, Entrapment efficiency and PDI of Efinaconazole loaded SLN formulations

Formulation code	Particle size (nm)	PDI	Zeta potential (mV)	Entrapment efficiency (%)
EF1	238.61 ±2.95	0.262±0.062	-37.6 ± 1.024	73.8±1.55
EF2	233.70±3.13	0.274±0.045	-28.1 ± 2.035	76.8±1.35
EF3	235.11 ±0.93	0.369±0.036	-39.4 ± 1.330	72.4±4.35
EF4	236.3 ± 1.89	0.365±0.044	-37.6 ± 2.065	71.3±2.45
EF5	234.9 ± 3.96	0.371±0.052	-39.2 ± 2.064	72.5±0.45
EF6	191.9 ± 3.23	0.270±0.056	-31.1 ± 1.050	77.9±0.55
EF7	235.0 ± 1.89	0.363±0.058	-39.0 ± 2.350	73.7±2.30
EF8	237.6 ± 1.92	0.375±0.052	-39.0 ± 1.035	71.8±3.45

*Data expressed as mean ± SD n=3

3.3.3 In-vitro Release Profile of selected batches of Efinaconazole drug loaded with Tween 80 and Palmitic Acid

Selected batches of Efinaconazole drug loaded with Tween 80 and Palmitic Acid shown 30% of drug release for all the batches within 1hour. There was 60% drug release was released slowly over a period of 6 hours. The batch EF1 shows about 77% of the Efinaconazole drug released at the end of 12 hours. From the figure, it observed that EF2, EF6 shows a drug release of 75% at the end of 12 hours. The increased lipid content material decreased the cumulative release, which is in support with the earlier reports. The packing density of lipid molecules increased and as a result release is decreased.

All the SLN formulations exhibited a burst type drug release in the first hour of dissolution and 30% of the release was observed. At the end of 6hrs 60% of drug release was observed from the formulations. Meanwhile, EF1 showed about 77.33% of Efinaconazole released at the end of 12 hours.

Table 5 In-vitro Release Profile of Efinaconazole for selected batches of Efinaconazole loaded SLN formulations

Time of Drug Release	EF1	EF2	EF3	EF4	EF5	EF6	EF7	EF8
0.5	36.66±1.56	41.75±3.42	39.76±2.46	39.83±0.18	39.32±2.56	42.56±2.20	34.67±2.48	35.66 ±3.07
1	41.66±1.44	45.18±2.64	43.55±1.64	46.5±1.36	44.46±1.42	46.88±1.46	40.46±1.12	47.89 ±0.84
2	57.99±2.76	51.14±2.16	49.03±3.41	52.44±2.72	53.68±0.34	54.76±3.28	53.67±1.02	56.66 ±0.56
4	62.88±0.18	58.39±3.04	54.99±1.16	56.37±1.16	55.67±2.88	56.88±0.26	59.77±0.56	64.72 ±1.92
6	66.44±0.48	63.55±1.62	59.52±2.22	59.46±3.24	62.24±1.16	63.74±1.29	62.29±0.34	66.68 ±3.63
8	71.54±0.44	70.15±1.16	66.41±2.48	64.82±0.28	63.24±0.64	70.42±0.19	66.24±0.66	68.42 ±2.46
12	77.33±0.52	75.14±2.37	74.43±1.16	73.85±2.63	75.54±3.34	75.34±2.54	73.54±2.64	74.44 ±1.20

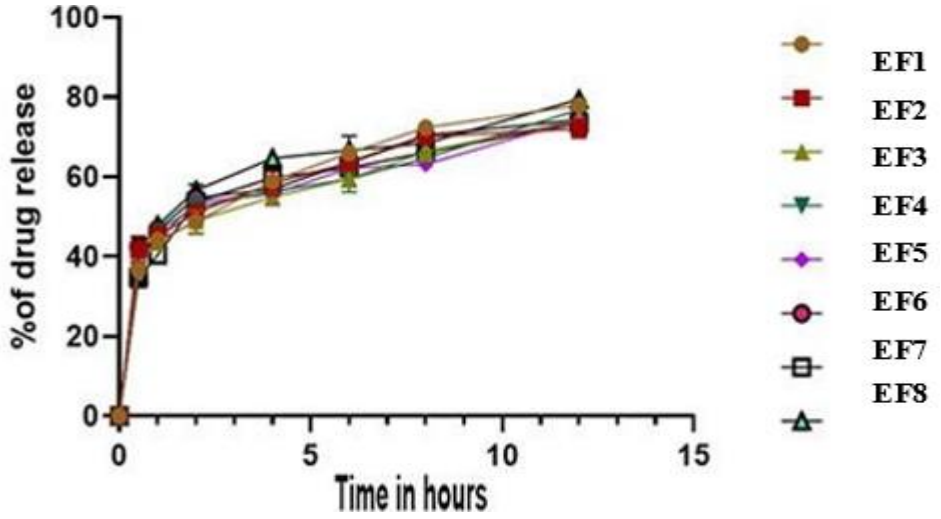


Figure 10 In-vitro Release Profile of Efinaconazole for selected batches of Efinaconazole loaded SLN formulations

Table 6 In-vitro Release Kinetics of Efinaconazole loaded SLN formulations

Formulation code	Zero order	First order	Korsemeyer-peppas	Korsemeyer n (Release exp)	Hixon Crowell	Higuchi Equation
EF1	0.7949	0.7556	0.9388	0.3308	0.7157	0.8681
EF2	0.867	0.7194	0.9839	0.1463	0.6756	0.8947
EF3	0.7203	0.6528	0.9631	0.3021	0.6141	0.8092
EF4	0.8132	0.6376	0.9947	o.1984	0.5956	0.8712
EF5	0.7315	0.614	0.9854	0.2246	0.5786	0.8144
EF6	0.7666	0.6536	0.9822	0.1818	0.6126	0.8104
EF7	0.8159	0.7447	0.9722	0.3152	0.7056	0.8907
EF8	0.782	0.7271	0.9756	0.334	0.6828	0.871

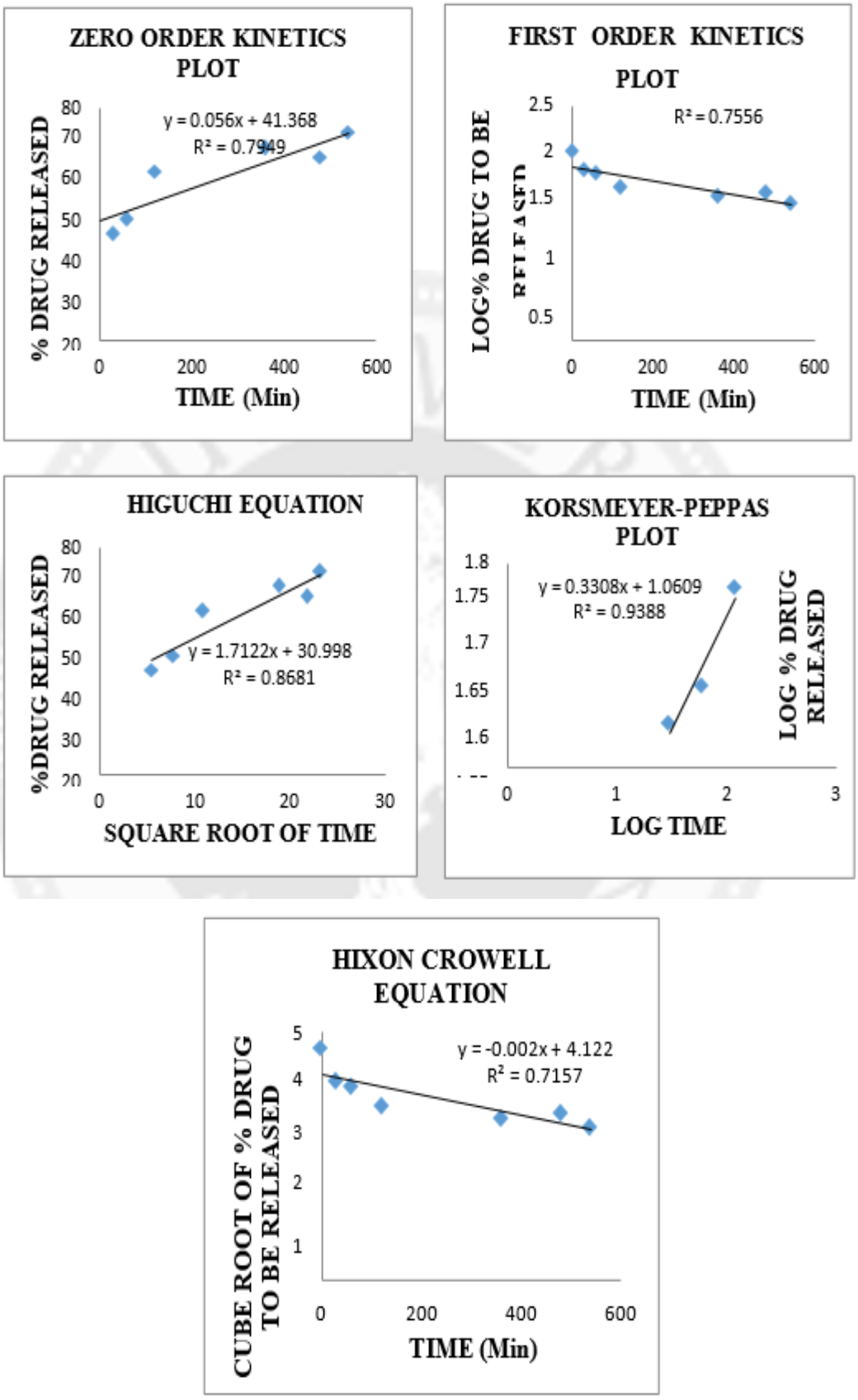


Figure 11 In-vitro release Kinetics of Efinaconazole EF1 formulation

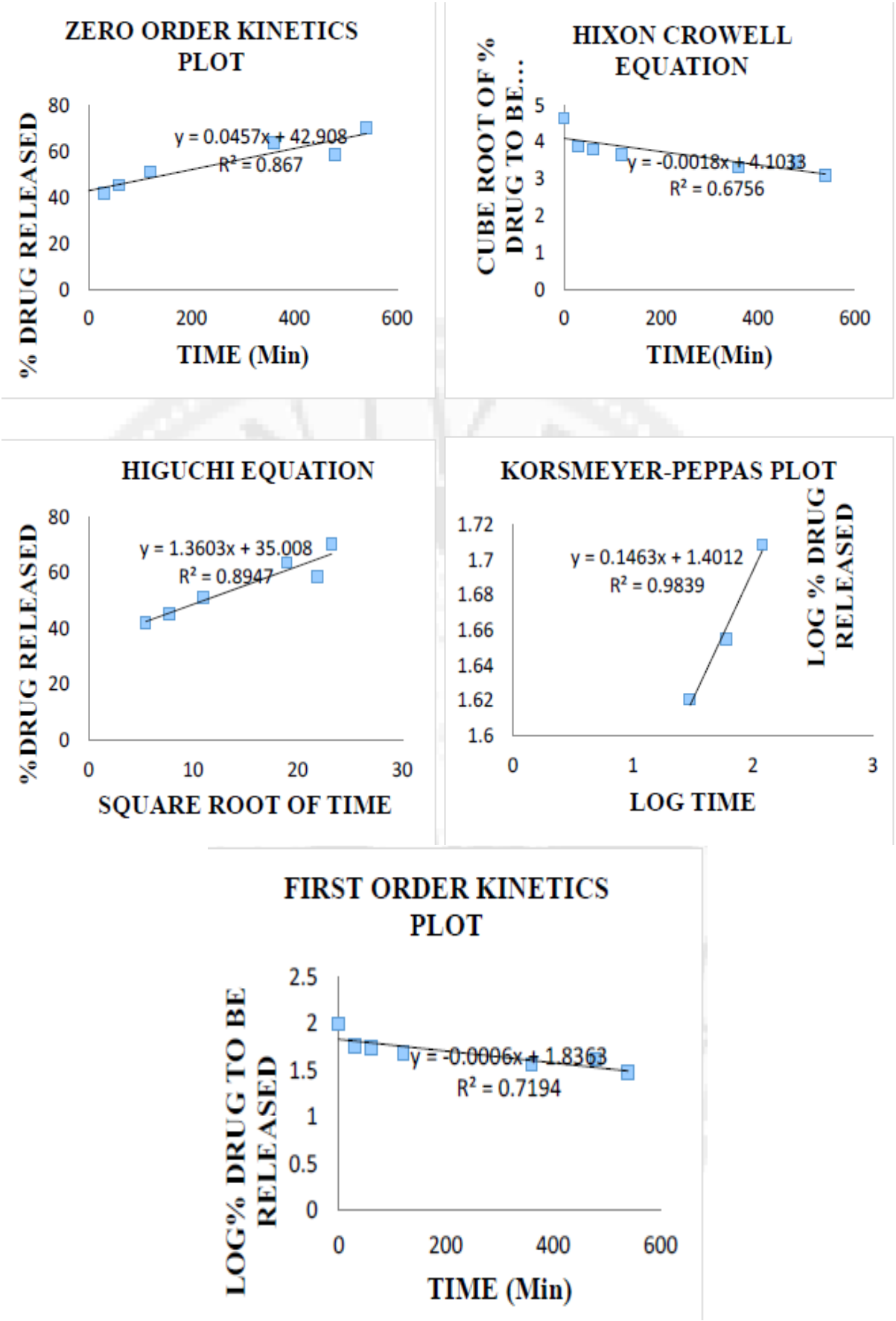
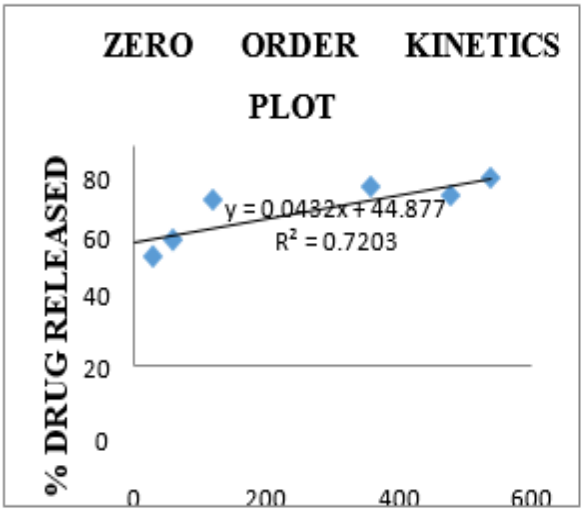
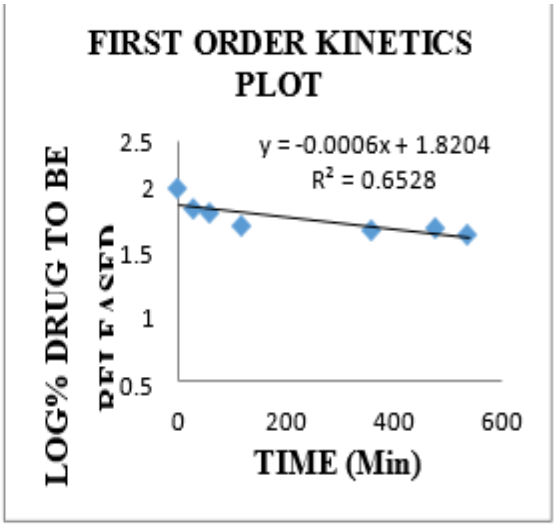
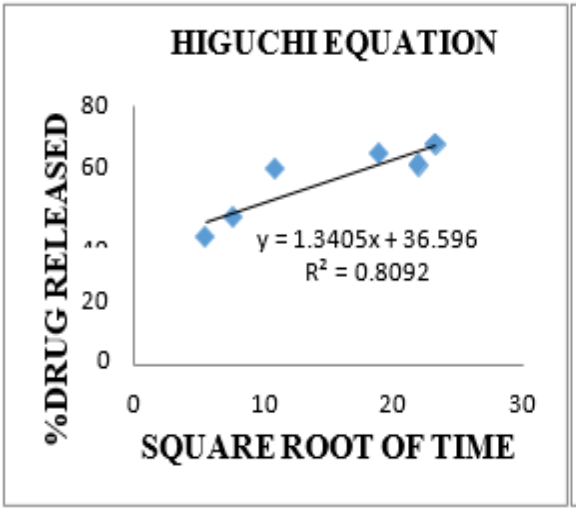
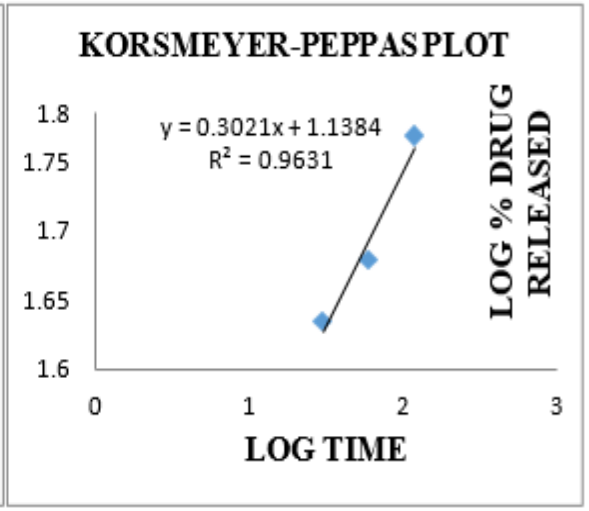


Figure 12 In-vitro release Kinetics of Efinaconazole selected EF2 Formulation









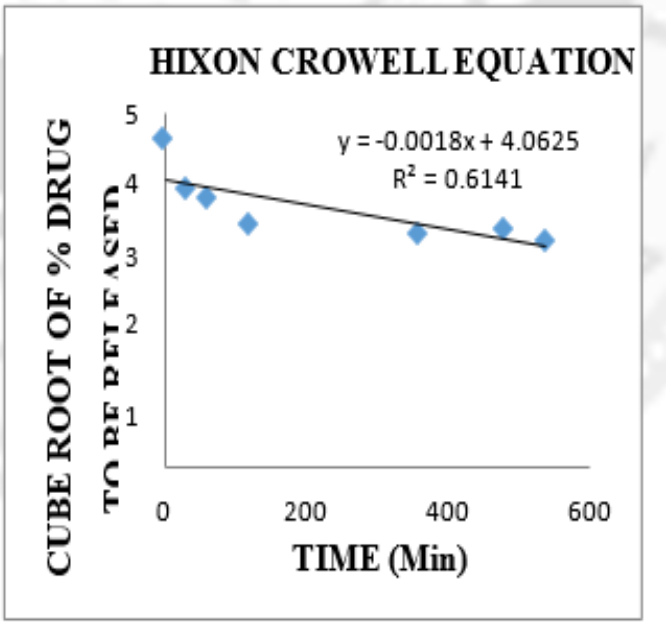


Figure 13 Invitro release Kinetics of Efinaconazole EF3 formulation

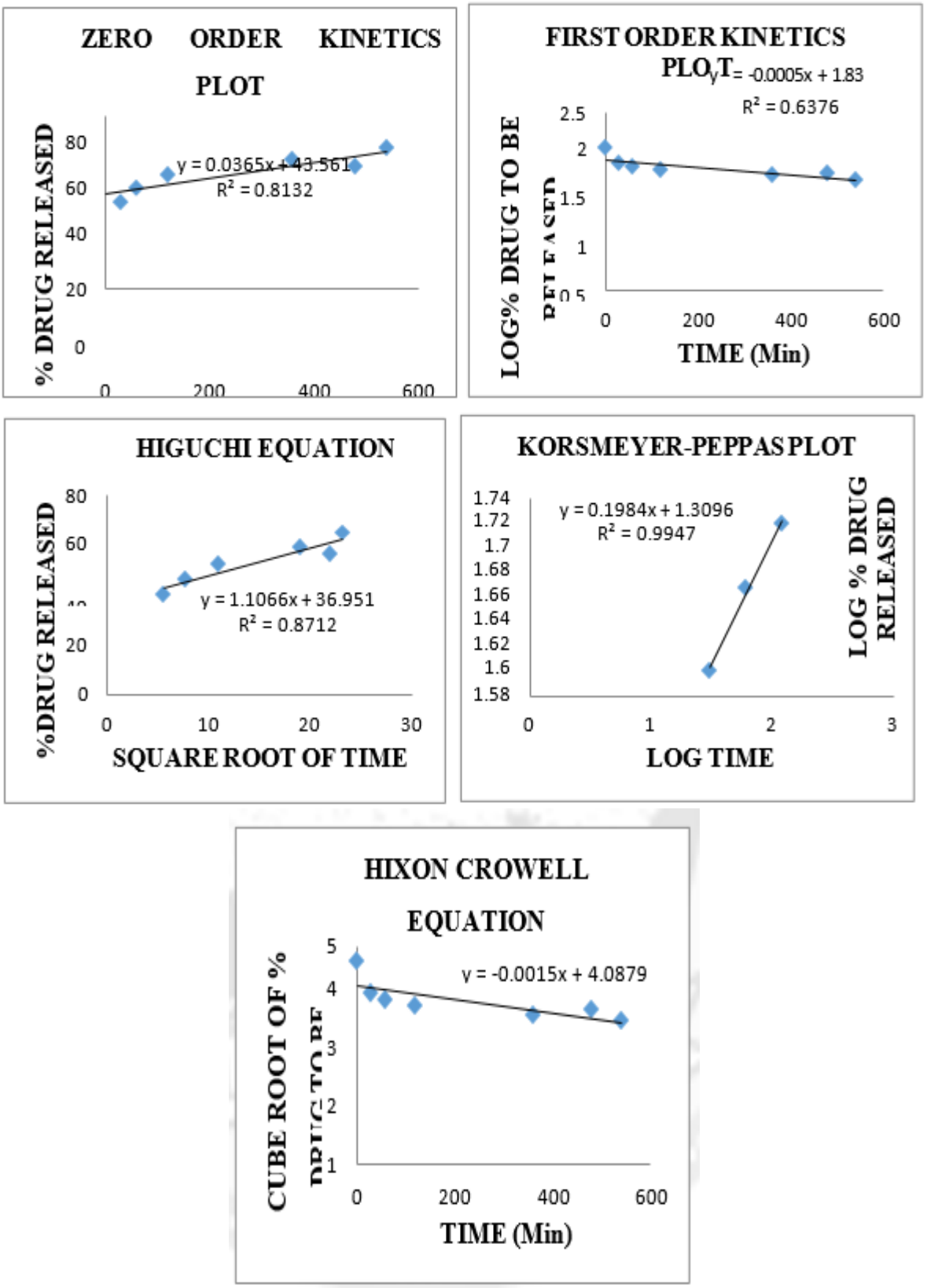


Figure 14 Invitro release Kinetics of Efinaconazole EF4 formulation

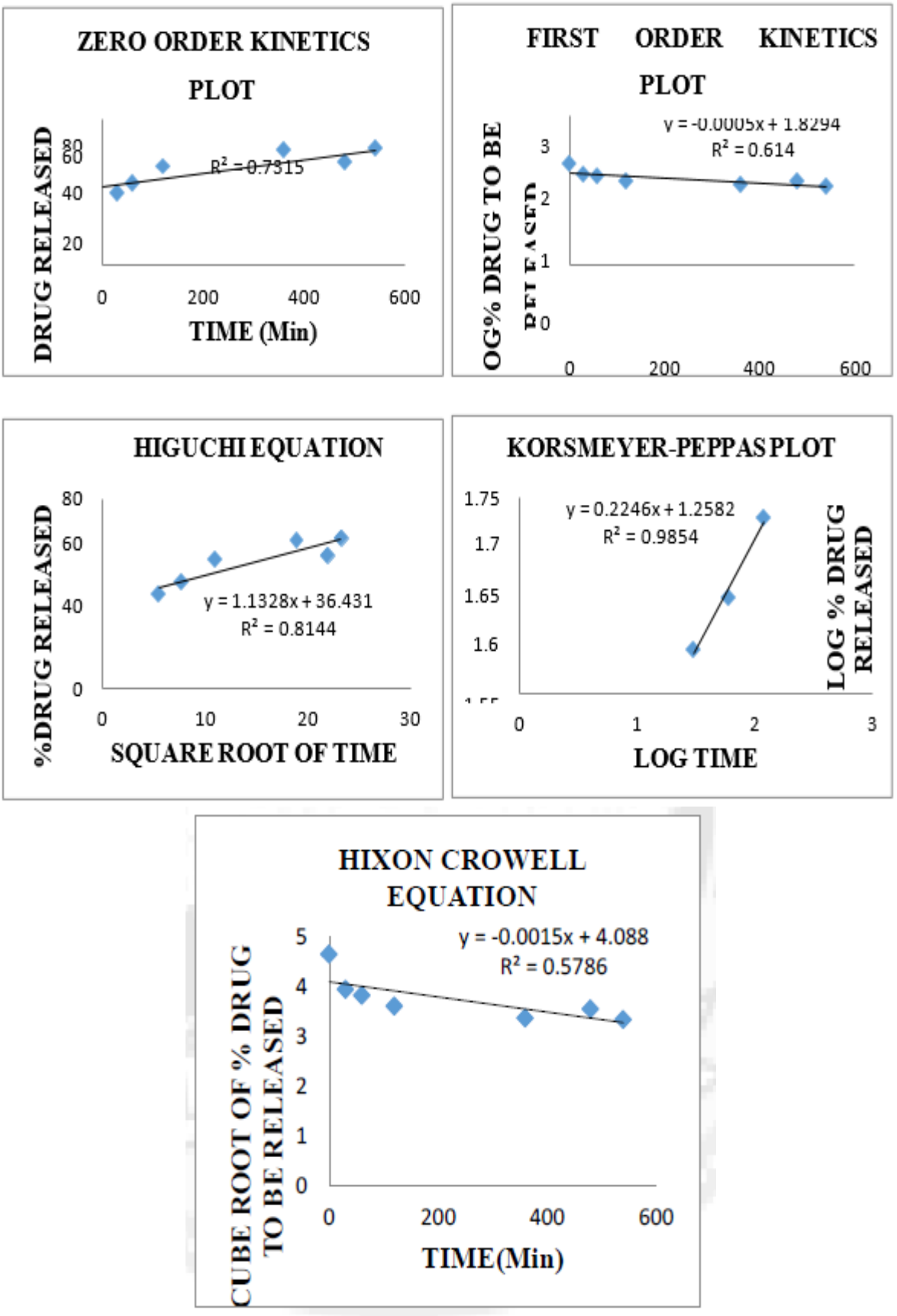


Figure 15 Invitro release Kinetics of Efinaconazole EF5 formulation

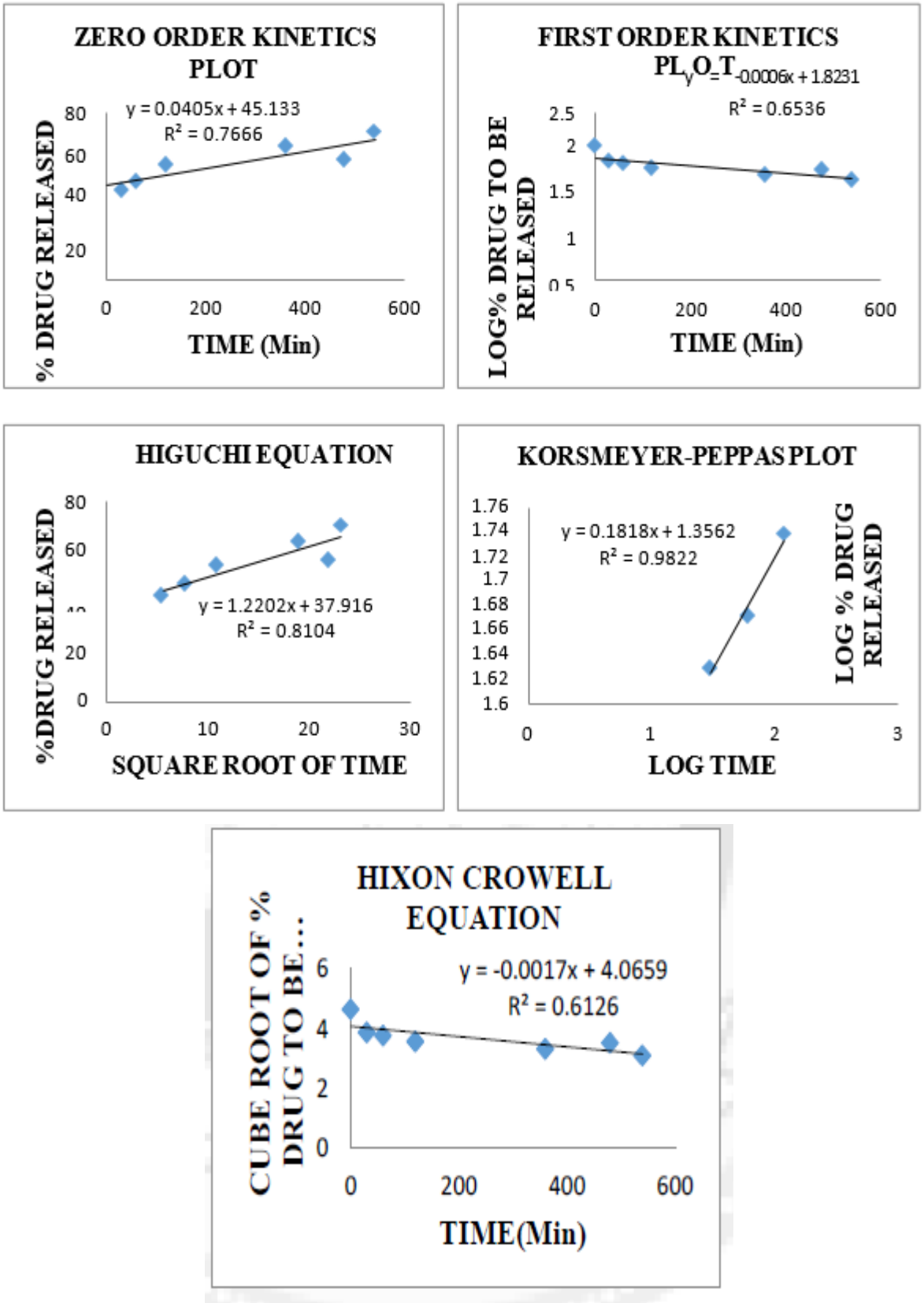
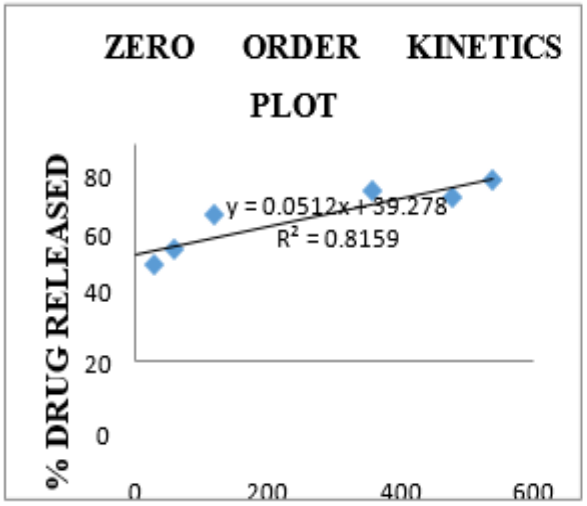
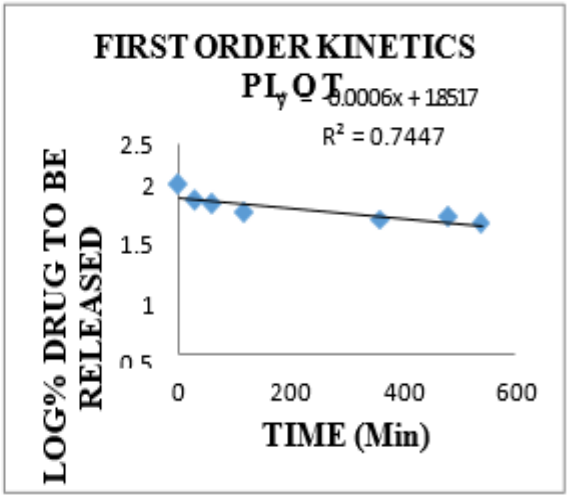
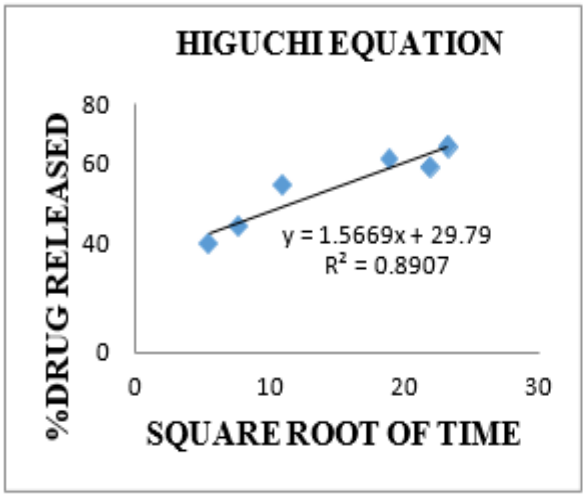
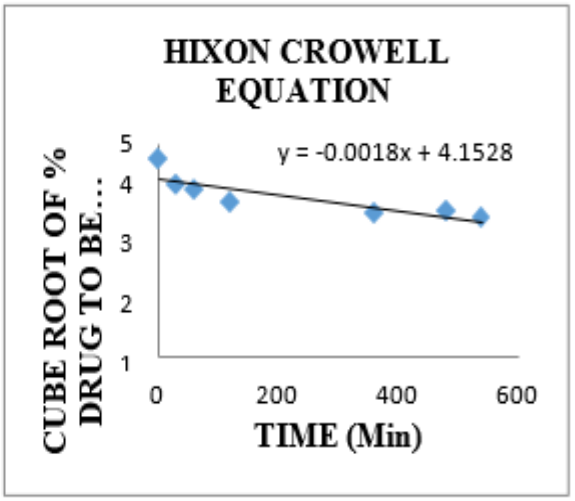


Figure 16 In-vitro release Kinetics of Efinaconazole EF6 formulation









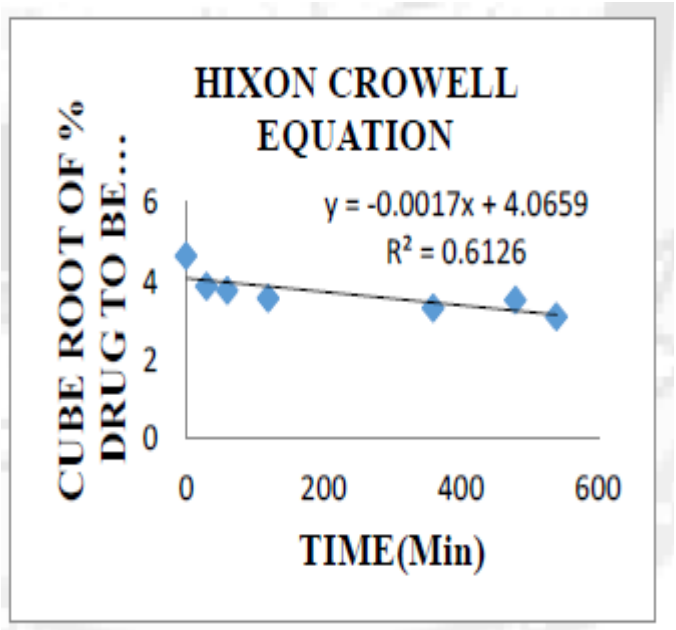


Figure 17 In-vitro release Kinetics of Efinaconazole EF7 formulation

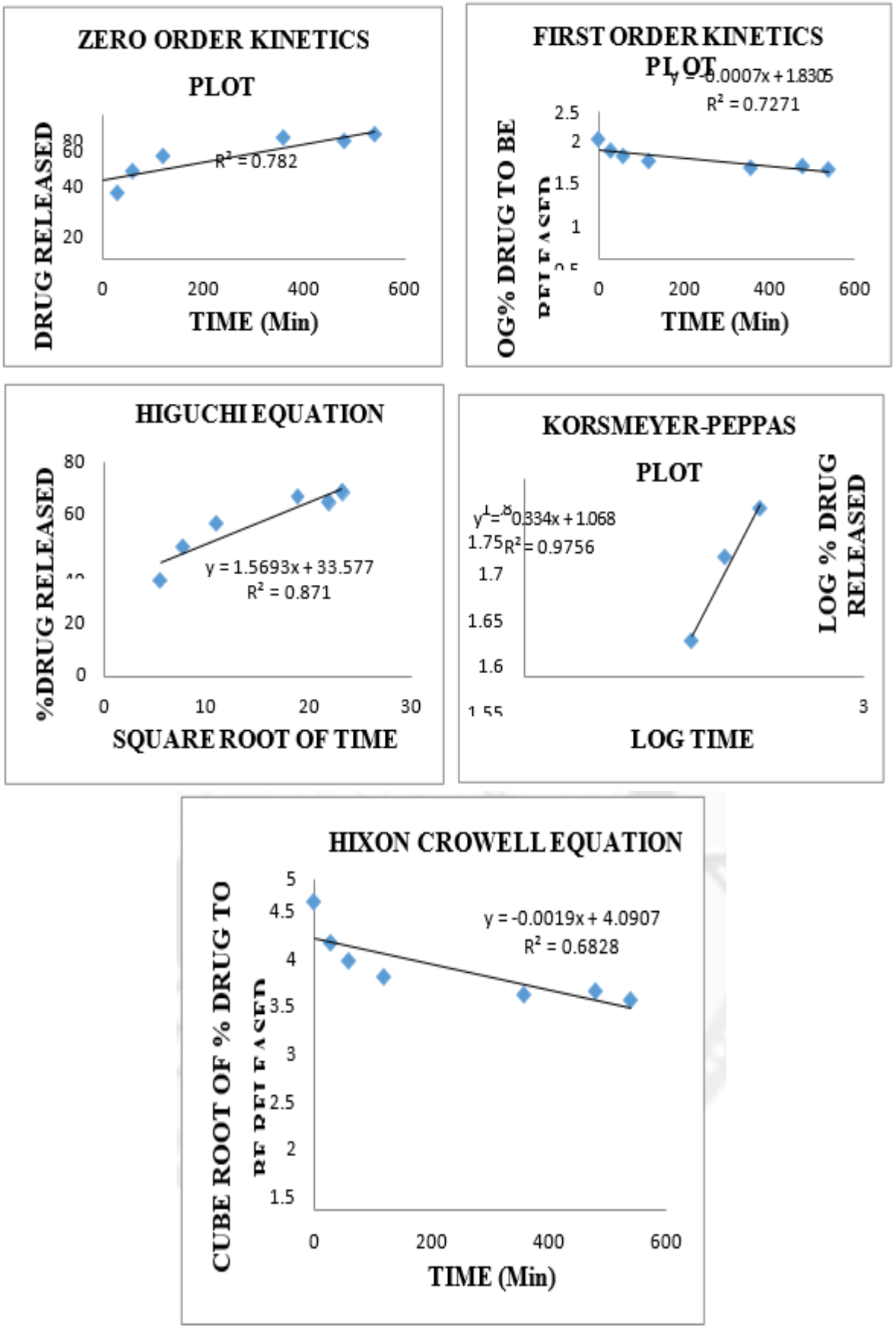


Figure 18 In-vitro release Kinetics of Efinaconazole EF8 formulation

3.3.4 Scanning electron microscopy (SEM)

The SEM studies were conducted to identify the topography of prepared SLN. Upon high resolution scanning, the SLN were observed to possess spherical morphology.

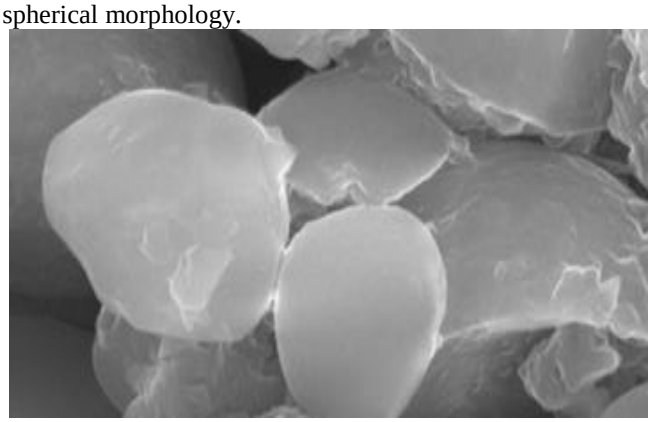


Figure 5 Scanning electron microscopy of Efinaconazole SLN EF2

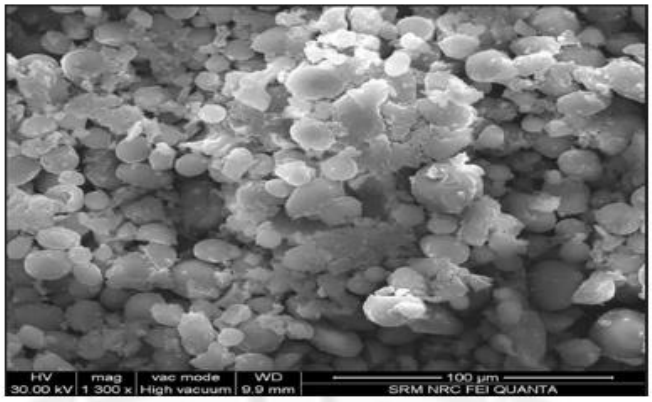


Figure 19 Scanning electron microscopy of Efinaconazole SLN EF6

3.3.5 Powdered X ray diffraction studies of selected Efinaconazole formulations

Powder X-ray analysis, of the Efinaconazole exhibited highly intense peaks and were characteristic of the API. Prominent peaks of pure drug Efinaconazole were observed at 2θ of 24, 93, 139, 162, 185, 208 and 231 were highly intense and indicated the crystalline nature. Whereas, in the prepared Efinaconazole SLN, the characteristic peaks of API were less intense. In addition, few low intense peaks were absent in the SLN, namely only one peak of pure drug at 162 to 350 was observed. These results clearly indicate the conversion of Efinaconazole to amorphous form. The similar results were observed in EF2, EF6 all the formulations of Efinaconazole indicating that the SLN preparation has resulted in the conversion of crystalline drug to its amorphous form.

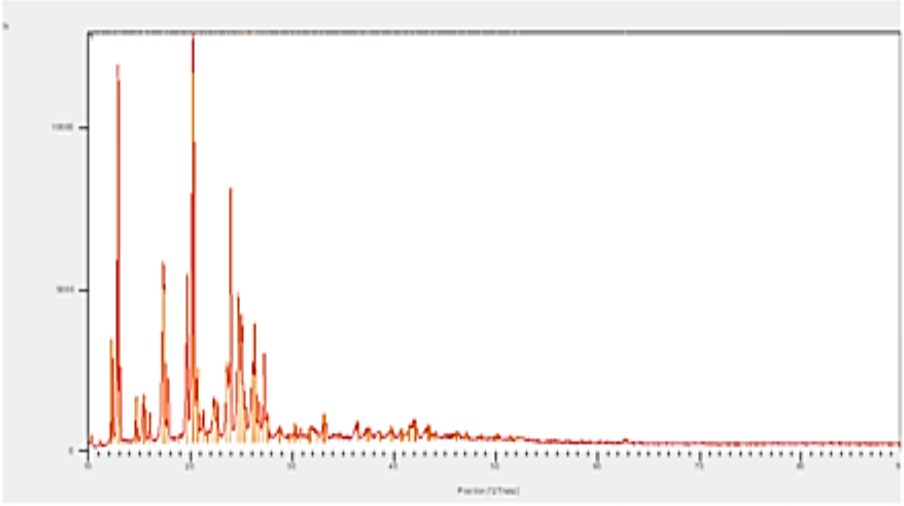


Figure 20 Powder X-ray Diffractions of Pure drug sample Efinaconazole

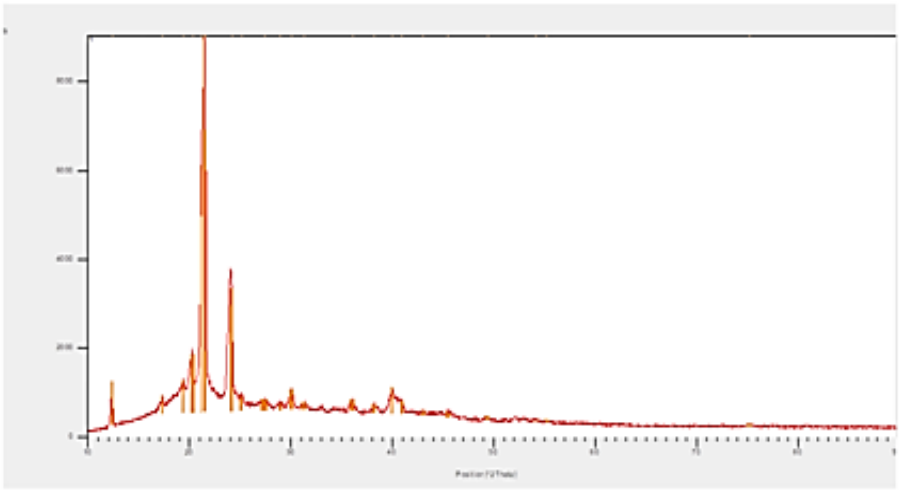


Figure 21 Powder X-ray Diffractions of selected Efinaconazole EF2 formulation

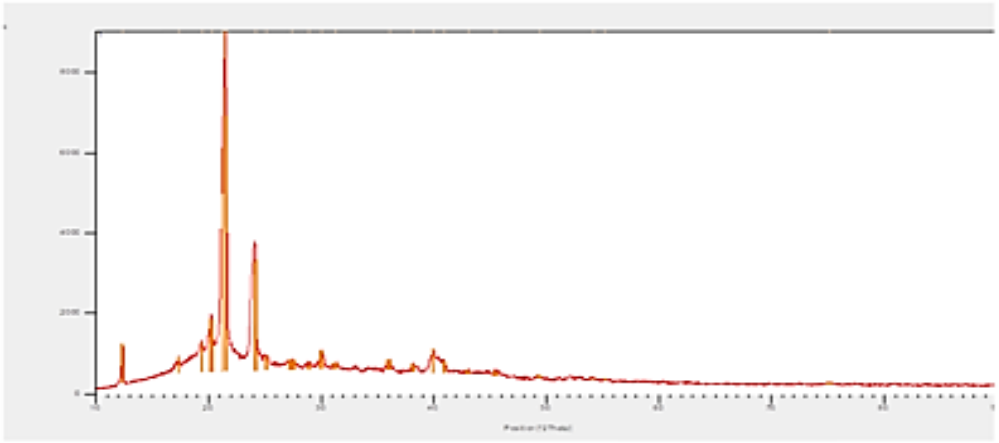


Figure 22 Powder X-ray Diffractions of selected Efinaconazole EF6 formulation

3.3.6 Transmission electron microscopy (TEM)

The TEM technique was used to analyses the morphology of prepared SLN. During TEM analysis, the particle was non-sticky to each other and were spherical shaped. It also confirmed that the prepared particles were of Nano range of 50-100 nm and in spherical shape.

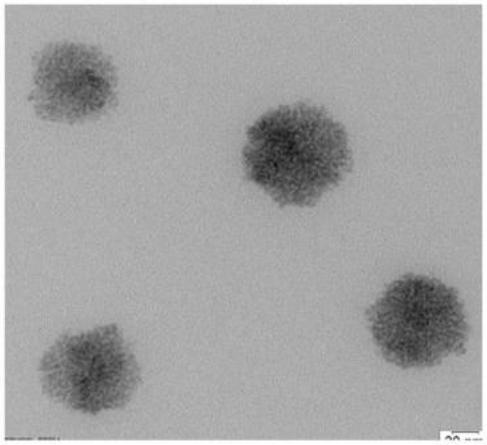


Figure 23 Transmission electron microscopy (TEM) of selected Efinaconazole EF2 formulation

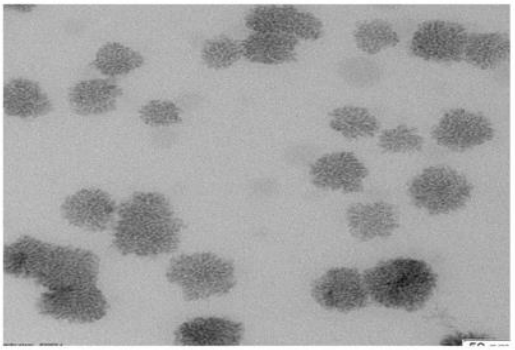


Figure 6 Transmission electron microscopy (TEM) of selected Efinaconazole EF6 formulation

3.3.7 Stability Study

The prepared SLN were stored at room temperature (28±2°C), refrigerated at 3-5° C for 6 months. To evaluate its stability. All the optimized formulations were stored in bottles and subjected to above mentioned temperatures at earlier mentioned temperature ranges. At the end of six months, the formulations were removed and evaluated for particle size and PDI. No marked difference in PDI and particle size was observed after 6 months and was mainly due to the lipid transition in the formulations and steric effect of Tween- 80 which enhanced the formulation stability.

Table 7 Stability Study data for the Formulation at initial, 3 and 6 months at room temperature and refrigerator temperature

Storage condition	Formulation code	Duration	Zeta size	Zeta potential	PDI	In-vitro drug release	Entrapment efficiency
Room temp	EF1	Day 1 Day 90 Day 180	238.71 239.87 245.87	-39.0 -39.4 -39.8	0.263 0.263 0.262	77.73 75.43 76.33	73.8 72.4 71.6
Room temp	EF2	Day 1 Day 90 Day 180	233.16 226.11 238.87	-34.40 -34.5 -34.87	0.369 0.383 0.394	75.80 74.44 73.21	76.8 75.4 75.02
Room temp	EF5	Day 1 Day 90 Day 180	234.41 235.22 236.87	-38.5 -38.7 -39.88	0.371 0.394 0.399	75.73 74.42 74.34	72.5 71.64 70.36
Room temp	EF6	Day 1 Day 90 Day 180	191.9 238.88 239.77	-30.2 -31.4 -32.87	0.270 0.273 0.281	75.22 74.12 73.36	77.9 76.4 75.2
Refri temp	EF1	Day 1 Day 90 Day 180	238.71 239.54 240.87	-39.2 -39.7 -39.87	0.263 0.263 0.261	77.73 76.43 76.33	73.8 73.04 72.69
Refri temp	EF2	Day 1 Day 90 Day 180	233.71 234.6 235.88	-32.44 -33.7 -34.87	0.274 0.276 0.278	75.80 75.44 74.21	76.8 75.7 74.9
Refri temp	EF5	Day 1 Day 90 Day 180	234.71 235.64 237.8	-38.0 -39.7 -39.87	0.371 0.373 0.385	75.73 74.42 74.34	72.5 71.8 71.11
Refri temp	EF6	Day 1 Day 90 Day 180	191.9 208.64 209.46	-31.9 -32.7 -32.87	0.274 0.280 0.281	75.22 75.12 74.36	77.9 77.46 76.24

4 SUMMARY AND CONCLUSION

The Solid lipid nanoparticles were successfully developed for Enhanced Solubility and Bioavailability of Poorly Soluble Efinaconazole Drug. SLN were formulated by High-shear hot homogenization and ultra-sonication method using stearic acid, Glyceryl monostearate, palmitic acid, and surfactants (1% and 2%). Physicochemical characterization including particle size, particle size distribution, Zeta potential, scanning electron microscopy, crystallinity study by DSC and in-vitro release profile were carried out. It was seen that increasing the stearic acid concentration led to higher entrapment and

by increasing the concentration of tween 80 lead to smaller the particle size. From the above experimental date, it can be concluded that a successful SLNs containing Efinaconazole have been developed (30).

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